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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/743,173	01/14/2002	Michela Seveso	P24376 USA	5272

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EXAMINER	
ANGELL, JON E	
ART UNIT	**PAPER NUMBER**
1635	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/743,173	SEVESO ET AL.	
	Examiner	Art Unit	
	J. E. ANGELL	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,44-52 and 55-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,44-52 and 55-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/8/2009 has been entered.

Claims 1, 44-52, 55-65 are currently pending in the application and are addressed herein.

Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1, 44-51, 55, 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO99/01579 (Teng et al., of record see IDS filed 1/7/2004).

WO99/01579 (TENG et al.) teaches a composition and method for enhancing the transport of a nucleic acid drug, especially antisense oligonucleotides, in an animal (e.g., see abstract). Teng et al. teaches that the composition that is administered to the animal comprises "various fatty acids… and other penetration enhancers" (e.g., see abstract); and specifically indicates that the fatty acid/penetration enhancer can be caprylic acid, including a sodium salt thereof (e.g., see page 10, lines 17-31; page 29, line 30 through page 30, line 25). Teng et al teach that the method can be used for delivery to the alimentary canal, including "any and all of its portions or segments, e.g.… the small and large intestines." (See page 7 lines 5-11). Teng et al. specifically teaches, "More specifically, the present invention is directed to the use of various fatty acids… and other penetration enhancers… to enhance the stability of oligonucleotides and other nucleic acids and/or their transport across and/or into cells of the alimentary canal." (Emphasis added, see page 1, lines 12-18). It is noted that oral administration of the composition would necessarily result in contacting epithelial cells of the small intestines with the composition which would be effective for facilitating the intracellular delivery of the nucleic acid. Teng et al also teach that the antisense oligonucleotide can comprise a modified backbone chemistry, such as a phosphorothioate modified backbone (e.g., see page 18). (Also see p. 17, lines 12-27; p. 29, line 30 through p. 30, line 30; claims 1-25, especially claims 1, 2, 4, 5, 14, 16, 25).

Teng et al also teaches that the enhancer can be caproate (C10), which is encompassed by claim 1, wherein the concentration of caproate is 1% of the solution (i.e., about 58mM). Furthermore, Teng et al teach that the composition was made by 500mg sodium caprate with 250ul of a solution containing 200mg/ml (i.e., 50mg) of an antisense oligonucleotide (see page 47 lines 4-9). Therefore, Teng et al teach that the molar ration of the enhancer (caprate) and the nucleic acid based drug (ISIS 2302) is within the range set forth in claim 55 (1:100 to 100:1).

It is noted that oral administration of the composition taught by Teng et al. must necessarily result in the intracellular delivery into the cytoplasm and/or nucleus of a cell resulting in homogenous distribution of the nucleic acid based compound in the cytoplasm and/or nucleus.

Although Teng teaches that the C10 enhancer can be used at a concentration of about 58mM, Teng does not teach to use "about 0.013mM to 13mM" of C10 enhancer, as is indicated in claim 1.

However, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to perform routine experimentation to determine the optimum and/or workable ranges of concentration for the C10 enhancer with a reasonable expectation of success.

As noted in In re Aller, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Accordingly, routine optimization is not considered inventive and no evidence has been presented that the selection the specific concentration range was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results

should be considered unexpected in any way as compared to the closest prior art. As such the instant claims are obvious in view of the teaching of Teng.

Claims 1 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO99/01579 (Teng et al., see above) in view of GB2319773A (Lewin et al., of record)

As indicated above, Teng et al teach that a composition comprising caprylic acid and a nucleic acid based drug can be used to deliver the nucleic acid based drug into a cell in a mammal.

Teng et al does not teach that the nucleic acid based drug is a gene coding for an RNA molecule which functions in an antisense capacity.

Lewin et al teach a nucleic acid vector which comprises a gene that express an RNA molecule which functions as an antisense oligonucleotide in a cell (e.g., see abstract, page 1, etc.).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the composition and method taught by Teng et al. such that nucleic acid was the vector taught by Lewin modified to express the antisense oligonucleotide taught by Teng et al. a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to make the modification because (1) Teng et al teach that the composition can be used for transporting nucleic acids into cells (e.g., see abstract; page 1; etc.) and (2) one of ordinary skill in the art would have recognized that the vector could be used to produce large amounts of the antisense RNAs in the

cell—larger amounts than would be delivered into the cell using the composition comprising the enhancer and an antisense oligonucleotide.

Claims 57, 58, 63, 64, 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO99/01579 (Teng et al., see above) in view of Akhtar (J. Drug Targeting 1998, of record)

WO99/01579 (TENG et al.) teaches a composition and method for enhancing the transport of a nucleic acid drug, especially antisense oligonucleotides, in an animal (e.g., see abstract). Teng et al. teaches that the composition that is administered to the animal comprises "various fatty acids… and other penetration enhancers" (e.g., see abstract); and specifically indicates that the fatty acid/penetration enhancer can be caprylic acid, including a sodium salt thereof (e.g., see page 10, lines 17-31; page 29, line 30 through page 30, line 25). Teng et al teach that the method can be used for delivery to the alimentary canal, including "any and all of its portions or segments, e.g.… the small and large intestines." (See page 7 lines 5-11). Teng et al. specifically teaches, "More specifically, the present invention is directed to the use of various fatty acids… and other penetration enhancers… to enhance the stability of oligonucleotides and other nucleic acids and/or their transport across and/or into cells of the alimentary canal." (Emphasis added, see page 1, lines 12-18). It is noted that oral administration of the composition would necessarily result in contacting epithelial cells of the small intestines with the composition which would be effective for facilitating the intracellular delivery of the nucleic acid. Teng et al also teach that the antisense oligonucleotide can comprise a modified backbone chemistry, such as a phosphorothioate modified backbone (e.g., see page 18). (Also see p. 17, lines 12-27; p. 29, line 30 through p. 30, line 30; claims 1-25, especially claims 1, 2, 4, 5, 14, 16, 25).

Teng et al does not teach that: (1) the oligonucleotide is complexed with a cationic lipid or a polymer system; (2) an endosomal escape/nuclear accumulation agent can be used to facilitate delivery; (3) a condensing agent can be used to condense the oligonucleotide and facilitate delivery; and (4) a condensing agent can be used to condense the oligonucleotide and the oligonucleotide is complexed with a cationic lipid to facilitate delivery.

However, Akhtar teaches a number of different means for facilitating delivery of antisense oligonucleotides into cells including the use of cationic lipids, polymer microspheres, as well as the use of agents to improve endosomal exit. Akhtar also teaches that polylysine, which one of skill in the art would recognize as a condensing agent, can improve cellular uptake of antisense oligonucleotides. (See page 228-230, section titled "Cellular Delivery of ODNs", including Table 1).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at he time of filing that any of the means of facilitating delivery of antisense oligonucleotides, taught by Akhtar (and combinations thereof) could be used to facilitate the delivery of the oligonucleotide compositions taught by Teng et al., with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to use those means for facilitating delivery of antisense oligonucleotides because Akhtar teaches that they improve cellular delivery of antisense oligonucleotides.

Claims 58-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO99/01579 (Teng et al., see above) in view of Akhtar (J. Drug Targeting 1998, of record) and Akhtar et al. (Int. J. Pharmaceutics, 1997, 151:57-67).

WO99/01579 (TENG et al.) teaches a composition and method for enhancing the transport of a nucleic acid drug, especially antisense oligonucleotides, in an animal (e.g., see abstract). Teng et al. teaches that the composition that is administered to the animal comprises "various fatty acids… and other penetration enhancers" (e.g., see abstract); and specifically indicates that the fatty acid/penetration enhancer can be caprylic acid, including a sodium salt thereof (e.g., see page 10, lines 17-31; page 29, line 30 through page 30, line 25). Teng et al teach that the method can be used for delivery to the alimentary canal, including "any and all of its portions or segments, e.g.… the small and large intestines." (See page 7 lines 5-11). Teng et al. specifically teaches, "More specifically, the present invention is directed to the use of various fatty acids… and other penetration enhancers… to enhance the stability of oligonucleotides and other nucleic acids and/or their transport across and/or into cells of the alimentary canal." (Emphasis added, see page 1, lines 12-18). It is noted that oral administration of the composition would necessarily result in contacting epithelial cells of the small intestines with the composition which would be effective for facilitating the intracellular delivery of the nucleic acid. Teng et al also teach that the antisense oligonucleotide can comprise a modified backbone chemistry, such as a phosphorothioate modified backbone (e.g., see page 18). (Also see p. 17, lines 12-27; p. 29, line 30 through p. 30, line 30; claims 1-25, especially claims 1, 2, 4, 5, 14, 16, 25).

Teng et al does not teach that: (1) the oligonucleotide is complexed with a cationic lipid or a polymer system; (2) an endosomal escape/nuclear accumulation agent can be used to facilitate delivery; (3) a condensing agent can be used to condense the oligonucleotide and facilitate delivery; and (4) a condensing agent can be used to condense the oligonucleotide and the oligonucleotide is complexed with a cationic lipid to facilitate delivery.

However, Akhtar teaches a number of different means for facilitating delivery of antisense oligonucleotides into cells including the use polymer microspheres. (See page 228-230, section titled "Cellular Delivery of ODNs", including Table 1).

Furthermore, Akhtar et al. (J Int Pharm, 1997) specifically teaches that biodegradable polymers, specifically PLGA, can be used to facilitate delivery of antisense oligonucleotides into cells, wherein the antisense oligonucleotide is complexed with (i.e., entrapped in) the polymer (e.g., see abstract).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing that antisense oligonucleotide composition (such as those taught by Teng) could be complexed with (entrapped in) a biodegradable polymer, such as PLGA (as taught by Akhtar et al.) to facilitate the delivery of the oligonucleotide compositions, with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to use the PLGA polymer of Akhtar et al. for facilitating delivery of the antisense oligonucleotide composition of Teng because Akhtar et al. teaches that PLGA improves cellular delivery of antisense oligonucleotides.

Claims 61 and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO99/01579 (Teng et al., see above) in view of Nakashima et al. (J. Pharm. Sci., 1995).

WO99/01579 (TENG et al.) teaches a composition and method for enhancing the transport of a nucleic acid drug, especially antisense oligonucleotides, in an animal (e.g., see abstract). Teng et al. teaches that the composition that is administered to the animal comprises

"various fatty acids… and other penetration enhancers" (e.g., see abstract); and specifically indicates that the fatty acid/penetration enhancer can be caprylic acid, including a sodium salt thereof (e.g., see page 10, lines 17-31; page 29, line 30 through page 30, line 25). Teng et al teach that the method can be used for delivery to the alimentary canal, including "any and all of its portions or segments, e.g.… the small and large intestines." (See page 7 lines 5-11). Teng et al. specifically teaches, "More specifically, the present invention is directed to the use of various fatty acids… and other penetration enhancers… to enhance the stability of oligonucleotides and other nucleic acids and/or their transport across and/or into cells of the alimentary canal." (Emphasis added, see page 1, lines 12-18). It is noted that oral administration of the composition would necessarily result in contacting epithelial cells of the small intestines with the composition which would be effective for facilitating the intracellular delivery of the nucleic acid. Teng et al also teach that the antisense oligonucleotide can comprise a modified backbone chemistry, such as a phosphorothioate modified backbone (e.g., see page 18). (Also see p. 17, lines 12-27; p. 29, line 30 through p. 30, line 30; claims 1-25, especially claims 1, 2, 4, 5, 14, 16, 25).

Teng et al does not teach that a P-glycoprotein inhibitor is administered with the antisense oligonucleotide composition.

However, Nakashima et al. teach that verapamil, a P-glycoprotein inhibitor, can be used in low doses in combination with antisense oligonucleotides to increase the efficacy of the antisense oligonucleotide treatment (e.g., see abstract).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to use verapamil, a P-glycoprotein inhibitor, in combination with antisense oligonucleotide composition taught by Teng, with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to use the P-glycoprotein inhibitor in combination with antisense oligonucleotide composition because Nakashima teaches that low doses of the inhibitor increases the efficacy of the antisense oligonucleotide.

Response to Arguments

5. Applicant's arguments have been fully considered and are persuasive in view of the amendment to the claims. Therefore, the previous rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made for the reasons set forth above.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. E. ANGELL whose telephone number is 571-272-0756. The examiner can normally be reached on Monday-Thursday 7:00 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tracy Vivlemore can be reached on 571-272-2914. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J. E. ANGELL/
Primary Examiner, Art Unit 1635